REMARKS

Claims 3, 35, 36 and 37 are pending, claims 6-34 are withdrawn, and claims 1, 2, 4, and 5 are canceled. Claims 3, 35, 36 and 37 have been amended. The amendments to the claims insert the term "amino acid" or "the amino acid sequence". These amendments do not add new matter.

Rejections Under 35 U.S.C. §§ 101/112, first paragraph

Applicants thank the Examiner for the telephone conferences with the undersigned and her associate, Dr. Margo Furman, on February 8, 2005, and April 6, 2005, regarding the rejection of claims 3 and 35-37 for lacking utility. During the telephone conferences, utilities for the claimed polypeptides as ligands for 5-HT_{2C} receptors were discussed. These utilities and others not previously discussed are set forth below.

Claims 3 and 36 are drawn to substantially pure polypeptides that include SEQ ID NO:1. Claims 35 and 37 are drawn to substantially pure polypeptides that include SEQ ID NO:2. The claimed polypeptides have multiple PDZ domains (specification, page 6, lines 10-24). Applicants asserted that the claimed polypeptides are involved, e.g., in neural transmission and malignant conversion and bind, e.g., to proteins that function in signal transduction in the cell (specification, page 2, lines 26-30). Thus, the claimed polypeptides are useful as receptors for proteins involved in processes such as neural transmission and malignant conversion (see, e.g., page 2, line 31, to page 3, line 3, and page 5, lines 1-4, of the specification) and for generating antibodies, e.g., to be used for identifying agents that modulate the processes (specification, page 19, line 29, to page 20, line 2).

In the Amendment filed on October 22, 2004, and in the telephone conferences with the Examiner, Applicants presented the asserted utilities and evidence for them in view of homology between the claimed polypeptides and a polypeptide disclosed in Ullmer et al. ("Ullmer"; *FEBS Letters*, 424:63-68, 1998; cited in the Information Disclosure Statement filed on May 10, 2002, and on page 2, line 16, of the specification). Ullmer isolated cDNAs encoding polypeptides containing sequences with a very high degree of homology to sequences of the claimed polypeptides. Ullmer's cDNAs were isolated in a screen for polypeptides that bind 5-HT_{2C}

receptors. 5-HT_{2C} receptors are serotonin receptors in the brain involved in a number of functions such as pain sensitivity and motor behavior. Ullmer's disclosure provides evidence that the claimed polypeptides exhibit features consistent with the asserted utilities, i.e., they are involved in neural transmission.

The Examiner stated that "the employment of a protein of the instant invention, in identifying compounds that agonize or antagonize activity of the 5-HT_{2C} receptor is not a credible, substantial or specific utility." No particular reason for the alleged lack of specificity or substantiality of this utility was provided, other than that it is "clearly prohibited by...judicial precedent since the compensation to the public is not commensurate with the monopoly granted. The instant protein has no demonstrated function." This is traversed.

As discussed in the Amendment filed on October 22, 2004, utilities of the claimed polypeptides for screening compounds that agonize or antagonize their binding to polypeptides involved in neural transmission, such as 5-HT_{2C} receptors, or for generating antibodies to be used in the methods, are specific because they are specific to the subject matter claimed and are not applicable to all proteins, or even all PDZ-domain-containing proteins. Example 12 of the USPTO Utility Guidelines Training Materials ("the Guidelines") states that methods of identifying materials which bind to a novel receptor and a method of making antibodies to the receptor are specific. The claimed polypeptides are receptors for polypeptides, as noted, e.g., at page 2, lines 21-26, of the specification. The claimed polypeptides interact with ligands through their PDZ domains. Thus, uses of the claimed polypeptides to identify compounds that modulate interactions with ligands such as 5-HT_{2C} receptors are "specific" utilities, as are uses to generate antibodies.

The utilities are substantial because they have a number of "real world" applications. Example 12 of the Guidelines explains that, to determine whether or not a method of identifying materials that bind to a receptor has a substantial utility, one must determine whether the material that binds to the receptor itself has a specific and substantial utility. Applicants have asserted that the claimed polypeptides are involved, e.g., in neural transmission and have provided evidence that they bind 5-HT_{2C} receptors. Modulation of 5-HT_{2C} receptor activity is known to

have pharmacological effects. For example, Clozapine, a drug used in treatment of schizophrenia, targets 5-HT_{2C} receptors. Because 5-HT_{2C} receptors are associated with specific, real world conditions, screening for interaction of polypeptides comprising SEQ ID NO:1 or SEQ ID NO:2 with ligands such as 5-HT_{2C} receptors is useful to identify agents that modulate (e.g., increase or decrease) that interaction, and this use has a substantial utility. Similarly, antibodies are useful as agents that modulate interactions between the claimed polypeptides and their ligands because the ligands, such as 5-HT_{2C} receptors, have specific and substantial utility. Further research is not required to identify a context of use for materials identified using the claimed polypeptides or antibodies thereto. Therefore, the standard for "substantial" utility is met.

The Examiner rejected Applicants evidence regarding the credibility of the utilities on the grounds that

> it is clear from the instant specification that the instantly claimed protein is what is termed an "orphan protein" in the art. As shown in Figure 2 of the instant specification, there is only 98% homology between a "portion" of the instant protein (from amino acid 921-1373) and the receptor protein of Ullmer et al. However, the Ullmer et al publication discloses that the MUPP1 protein which is a member of the PDZ protein family interacts with the C-terminus of the 5-HT_{2C} receptors, i.e., the PDZ domain protein MUPP1 is a scaffolding protein that interacts with the 5-HT_{2C} receptor. This disclosure in the post-filing reference was not disclosed in the present application as filed.

The Examiner dismissed Applicants' evidence that the claimed polypeptides bind 5-HT_{2C} receptors on the ground that Figure 2 of the specification shows an alignment of only a portion of SEQ ID NO:1 and a human amino acid sequence isolated by Ullmer. The Examiner implied that an asserted utility based on binding to 5-HT_{2C} receptors is incredible because the homology over only a portion of the polypeptides is not significant. This rationale for dismissing this evidence is improper for at least two reasons.

First, the homology within the regions shown in Figure 2 is significant in and of itself, regardless of the level of homology outside of those regions. As was discussed during the telephone conferences, a polypeptide consisting of Ullmer's sequence shown in Figure 2 binds 5-HT_{2C} receptors (Ullmer, page 65, left col., first paragraph). Ullmer's sequence shown in

Figure 2 is a fragment of the human MUPP1 polypeptide. A single PDZ domain within this fragment, PDZ10, was later shown to mediate binding to 5-HT_{2C} receptors (see abstracts of Becamel et al., *J Biol Chem.*, 276(16):12974-12982, 2001; and Parker et al., *J Biol Chem.*, 278(24): 21576-21583, 2003; provided as Exhibits A and B, respectively, with the Amendment filed on October 22, 2004). PDZ10 includes amino acid residues 7-95 of the lower sequence in the alignment shown in Figure 2 of the specification. Both rat and human MUPP1 bind 5-HT_{2C} receptors (see Ullmer and Becamel et al.). The presently claimed polypeptides have a domain identical to PDZ10 of human MUPP1 at all but one amino acid residue, F957 of SEQ ID NO:1. The claimed polypeptides have a domain identical to PDZ10 of rat MUPP1 (which also binds human 5-HT_{2C} receptors) at all but two amino acid residues, R939 and F957 of SEQ ID NO:1.

A utility should not be dismissed as lacking credibility unless based on seriously flawed logic, or unless based on facts inconsistent with the logic underlying the asserted utility. PDZ domain-containing polypeptides are modular, protein-binding scaffolding molecules. Each PDZ domain within these polypeptides independently mediates interactions with other polypeptides. The evidence that the claimed polypeptides possess a domain identical (but for a single or double amino acid change) to a domain critical for binding to 5-HT_{2C} receptors is based on facts and is consistent with the well-known role of PDZ domain-containing proteins as modular protein-binding receptors. No evidence has been provided to the contrary. Therefore, the assertion that the claimed polypeptides are involved in neurotransmission, e.g., by binding to 5-HT_{2C} receptors, is credible.

Second, Applicants direct the Examiner's attention to Figures 3 and 4 of the specification, which depicts an alignment of the full length of SEQ ID NO:1 with rat MUPP1 (deposited under GenBank® Acc. No. AJ001320). As evident from Figures 3 and 4, SEQ ID NO:1 shares a high degree of homology with rat MUPP1 along its entire length. Although Applicants do not agree that evidence of homology across the entire length of the sequence should be necessary to support a utility based on the function of a single domain within the claimed sequences, such homology clearly exists and is demonstrated in Figures 3 and 4 of the specification. Thus, the asserted utilities for the claimed polypeptides are supported by both the

high degree of homology within a domain critical for that function as well as a high degree of homology over the full length of the polypeptide. Applicants have thus shown that the asserted utilities are credible.

In the Amendment filed on October 22, 2004, Applicants also noted that the claimed polypeptides have well established utilities as tissue markers and as agents to generate antibodies for detecting liver cells and lung cancer tissues. The Examiner stated:

> [T]he employment of the claimed polypeptide in such a method is not a substantial or specific utility because the instant polypeptide has not been shown to be differentially expressed in normal and lung tumors...All human proteins can invariably be classified into two categories, those which are expressed in a tissue or developmentally specific manner and those which are expressed ubiquitously. It can be alleged that any protein which is expressed in a tissue specific manner can be employed to detect the tissue in which it is expressed in a sample...Such utilities are analogous to the assertion that a particular protein can be employed as a molecular weight marker, which is neither a specific or substantial utility.

This reasoning is not understood. Applicants have identified a number of narrowly drawn utilities, including use as a marker for liver cells or lung tumor cells. These are no less "specific" than the utility as a marker for cancer cells lauded by the Guidelines (Example 12, page 70) as adequate. The fact that some other proteins are expressed in a tissue specific matter, while some aren't, is completely irrelevant to the question of whether the particular utility identified by Applicants is "specific". Since use as a liver cell marker or lung tumor marker is not a utility applicable to the general class of the invention (i.e., all polypeptides), it is "specific". This is not the type of "unspecified" or "general statement" of utility that the Guidelines say would be insufficient, because Applicants have indicated the tissue type and tumor type that can be identified. These are not analogous to "throw away" utilities because they are not applicable to every protein or even every PDZ domain-containing protein. A "specific" utility need not be a novel utility, nor one based on an enzymatic function.

The Office action also alleges that use as liver cell or lung tumor cell markers is not a substantial utility. The Guidelines provide that an assay that measures the presence of a material

which has a stated correlation to a particular condition defines a "real world" context of use in identifying potential candidates for preventive measures or further monitoring. Similarly, expression of the claimed polypeptides has a stated correlation to a particular disease condition: lung cancer. They are clearly useful for monitoring or detecting lung cancer. Liver markers are similarly useful, e.g., for distinguishing liver cells from invasive, metastatic non-liver cells for histopathology. Because the contexts in which the polypeptides are useful is immediately apparent from their tissue- and tumor-specific expression, and the uses to which they can be put have "real world" implications, the standard for "substantial" utility is met.

The Examiner also asserted that the utilities as tumor markers are not credible. *The credibility of using the claimed polypeptides as liver markers was not even addressed, so apparently is implicitly acknowledged.* The specification shows that the claimed polypeptides are expressed in a tissue- and tumor-specific manner (see, e.g., Example 5 on pages 46-47, and Figure 6). Despite Applicants' evidence of this differential expression, evidence stressed in the prior response, the Office action merely states (without explanation) that "the instant polypeptide has not been shown to be differentially expressed in normal and lung tumors." No reason has been provided to doubt the credibility of Applicants' facts. An Examiner must provide an explanation that clearly sets forth the reasoning used in concluding that the asserted specific and substantial utility is not credible; support for factual findings relied on to reach this conclusion; and an evaluation of all relevant evidence. MPEP 2107.2. If the Examiner intends to maintain her position that use of the claimed polypeptides as tumor-specific markers as not credible, Applicants request that this explanation be provided. Further, Applicants request that the Examiner either acknowledge explicitly that the utility as a liver cell marker is credible, or elucidate why she believes otherwise so that Applicants can respond.

The claimed polypeptides possess additional well-established utilities not previously discussed with the Examiner. These utilities would have been apparent to one of ordinary skill reading the disclosure of the application at the time the application was filed. As described in Example 4 of the specification (beginning at page 45, line 5), the inventors performed BLASTN and BLASTP searches to identify sequences homologous to the novel sequences. These searches

revealed that the claimed polypeptides are homologous to *Mus musculus* 9ORF binding protein-1 (9BP-1), deposited under GenBank® Accession No. AF000168 (specification, page 45, lines 7-10). Figure 1 of the specification depicts an alignment between a portion of SEQ ID NO:1 and 9BP-1. The portions of SEQ ID NO:1 and 9BP-1 shown in Figure 1 are identical at all but 71 amino acid positions, which is more than 86% of the residues. Prior to filing of the present application, 9BP-1 was identified as a polypeptide that binds to an adenovirus oncoprotein, the 9ORF1 gene product, as shown by Lee et al., *Proc. Natl. Acad. Sci. USA*, 94:6670-6675, 1997 (copy attached as Exhibit A; "Lee 1"). Lee 1 showed that 9BP-1 binds the adenovirus oncoprotein but not a transformation-defective mutant of the oncoprotein (Lee 1, abstract, lines 3-7; and page 6671, left column, last paragraph). Thus, not only does a close homolog of the claimed polypeptides bind to an oncoprotein, but its binding correlates with function (i.e., transformation), because a transformation defective form of the oncoprotein does not interact with the homolog. This is evidence that the murine polypeptide mediates the transforming activities of the oncoprotein. Various utilities would have been apparent to one of ordinary skill from the disclosure of the homology of the claimed polypeptides to 9BP-1. These include uses in isolating the oncoprotein, identifying compounds that block transforming activity of the oncoprotein (e.g., by interfering with binding of the oncoprotein to the claimed polypeptides), or identifying compounds that block any another activity of the oncoprotein.

These utilities are specific because they are specific to the subject matter claimed. They are not applicable to all proteins (or even all PDZ domain-containing proteins). They are substantial because they have a number of "real world" applications, including the uses discussed immediately above (e.g., isolating the oncoprotein and identifying compounds that block interaction with the oncoprotein). As the Examiner is no doubt aware, methods or agents for identifying materials that have a specific and substantial utility are recognized by the Guidelines as meeting the "substantial" requirement. That is the case here. Oncoproteins have specific and substantial utilities, e.g., as agents for transforming cells or for finding compounds that inhibit their actions. Finally, these utilities are credible because they are based on facts and logic consistent with the facts. 9BP-1 binds to a viral oncoprotein, 9ORF-1, as shown in Lee 1. SEQ

ID NO:1 and SEQ ID NO:2 have a very high degree of homology to 9BP-1, as shown in Figure 1 of the specification. Applicants note that 9BP-1 is a murine polypeptide and the claimed polypeptides are human. The high degree of homology between the sequences is even more significant in view of the species difference. Later-published work lends further support to the evidence that the claimed polypeptides bind the same viral oncoprotein. Lee et al. (*J. Virol.*, 74(20):9680-9693, 2000; "Lee 2"; copy attached as Exhibit B) showed that 9BP-1 is mouse MUPP1 (and that 9BP-1 disclosed in Lee 1 was actually only a fragment of the full-length 9BP-1/MUPP1)(Lee 2, page 9682, right column, line 2, to page 9684, right column, line 23). As noted in the discussion regarding utilities as polypeptides that bind 5-HT_{2C} receptors, the claimed polypeptides are highly homologous to rat MUPP1 across their entire length. The fact that the claimed polypeptides exhibit a high degree of homology to rat and mouse MUPP1 lends further credibility to the contention that they share functions with those polypeptides, such as binding to viral oncoproteins.

Because Applicants have shown that the claimed polypeptides have a number of specific, substantial, and credible utilities, withdrawal of the rejections of claims 3 and 35-37 as lacking utility is respectfully requested.

Rejections Under 35 U.S.C. §112, second paragraph

Claims 3 and 35-37 were rejected as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Applicants believe that these claims as written were sufficiently clear because they include the word "polypeptide", but have nonetheless amended the claims as suggested, to further include the term "the amino acid sequence of" prior to each SEQ ID NO in the claims. This amendment does not change the scope of the claims. Withdrawal of the rejection is requested.

Enclosed is a check for the Petition for Extension of Time fee. Please apply any other charges or credits to deposit account 06-1050, referencing attorney docket no. 14875-056001.

Respectfully submitted,

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